

Nephrotic syndrome in a patient with metastatic melanoma: beyond the obvious

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ABSTRACT

Nephrotic syndrome in a patient with metastatic melanoma can occur in the context of a paraneoplastic glomerulopathy or as a complication of treatment. New oncologic immunotherapies, including immune checkpoint inhibitors, have been frequently associated with interstitial nephritis and, in rare cases, with nephrotic syndrome. This article presents the case of a 52-year-old man diagnosed with metastatic melanoma who was admitted with acute kidney injury and nephrotic syndrome after having started immune checkpoint inhibitors. After investigation, acute kidney injury was attributed to immunotherapy-associated acute interstitial nephritis, and nephrotic syndrome was found to be the result of AA amyloidosis, which is a rare complication of metastatic melanoma.

Key-Words: amyloidosis, immunotherapy, melanoma, nephritis

INTRODUCTION

The approach to a patient with malignant tumor and kidney disease is complex since the disease etiology can have multiple causes. In addition to paraneoplastic glomerulopathies or direct kidney invasion by tumor cells, oncologic drug nephrotoxicity plays an important role in renal damage.

In the setting of nephrotic syndrome and malignant tumor, membranous glomerulopathy is the most common diagnosis¹, which can be the first manifestation of tumor². Nephrotic syndrome can also occur as an iatrogenic complication of cancer immunotherapy, including interferon therapy³. More recently, there have been case reports of nephrotic syndrome caused by immune-checkpoint inhibitors (ICPIs), mainly in the setting of minimal change disease^{4,5,6}.

ICPI therapy is an immunotherapeutic strategy which, instead of targeting tumor cells directly as chemotherapy, interferes with of cancer cells' ability to avoid an attack by the immune system, reinvigorating pre-existing anticancer immune responses⁷. ICPIs inhibit intrinsic down-regulators of T cells, such as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein-1 pathway (PD-1) or its ligand (PD-L1)⁸. In the last decade, they have been approved by the US Food and Drug Administration (FDA) for the treatment of several malignant tumors, with promising outcomes⁹.

Although their tolerance seems to be better than chemotherapy¹⁰, ICPIs can cause immune-related adverse events (irAEs) in off-target organs, via several mechanisms which remain to be elucidated¹¹. More than 50% of patients develop an irAE, which is severe or life-threatening in approximately 20% of cases¹². Skin, gastrointestinal tract and

endocrine glands are most commonly involved⁹. Nephrotoxicity is a rare complication, with acute kidney injury (AKI) due to acute interstitial nephritis (AIN) the most commonly documented lesion^{13,14}. Its incidence has been reported as low as 1.4% with monotherapy and up to 4.9% when combination therapy has been used¹⁵. The incidence of grade III and IV AKI (defined as the need for hospitalization or for urgent dialysis, respectively, according to National Cancer Institute Common Terminology Criteria for Adverse Events¹⁶) was 0.6%¹⁵.

Renal biopsy plays an important role in identifying the underlying kidney disease in the setting of malignant tumor, which is essential for therapeutic decision and prognosis.

The authors report a case of a 52-year-old caucasian male patient displaying metastatic melanoma and kidney disease which manifested as AKI and nephrotic syndrome.

CASE REPORT

A 52-year-old man with an history of malignant melanoma diagnosed over 20 years ago, initially treated with surgery and chemotherapy, has been regularly followed by an oncologist. In the last 2 years, lung and lymph nodes metastatic involvement were identified and the patient was submitted to radiotherapy, chemotherapy and immunotherapy with ipilimumab (an intravenous monoclonal antibody against CTLA-4 administered at 3 mg/Kg every 3 weeks until completing 4 cycles). Unfortunately, disease control was poor with subsequent positron-emission tomography diagnosis of tumor invasion of liver and bones four months later. After one year with rescue therapy with nivolumab (an intravenous anti-PD-1 monoclonal antibody

administered at 240 mg every 2 weeks), the patient was referred to our nephrology clinic for the evaluation of AKI [serum creatinine (Scr) rising from 0.9 to 2.2 mg/dL [normal range (NR) 0.72 – 1.25 mg/dL] between February and April]. Additional significant medical history included lisinopril therapy for systemic hypertension (diagnosis 5 years ago; no history of vascular complications) and diagnosis of kidney stones with acute colic episode 4 years ago. In the last few months, along with omeprazole, the patient was receiving celecoxib therapy to control rib pain and has recently been submitted to radiotherapy to limit rib metastatic injury. On presentation, blood pressure was 115/80 mmHg, pulse rate 75 beats/min and his physical examination

revealed a bilateral lower-extremity oedema, without fever, skin rash or pruritus. Chest auscultation and abdomen palpation were normal. Laboratory tests demonstrated normocytic normochromic anemia (hemoglobin 10.2 g/dL, NR 13 – 17 g/dL), Scr 4.4 mg/dL, without electrolyte or acid-base disturbances; normal hepatic function, hypoalbuminemia (serum albumin 2.97 g/dL, NR 3.2 – 4.6 g/dL), hypercholesterolemia [total serum cholesterol 305 mg/dL (NR < 190 mg/dL) and triglycerides 467 mg/dL (NR < 150 mg/dL)] and nephrotic range proteinuria (a urine protein-to-creatinine (UPC) ratio of 20561 mg/g, NR ≤ 200 mg/g). In addition to proteinuria, urinalysis showed sterile pyuria with 23 white blood cells per cubic millimeter (mm^3) (NR < 11

Figure 1

PAS [Periodic Acid–Schiff], x200
Glomerular and vascular amorphous material deposits.

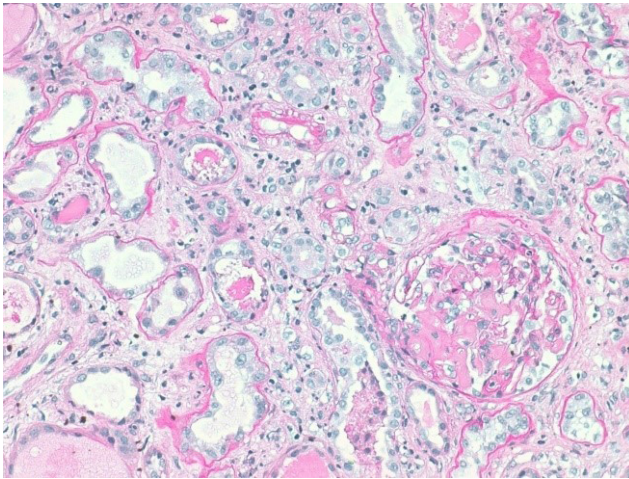


Figure 2

Congo red, x200
Amorphous material deposits were identified as amyloid by Congo red staining.

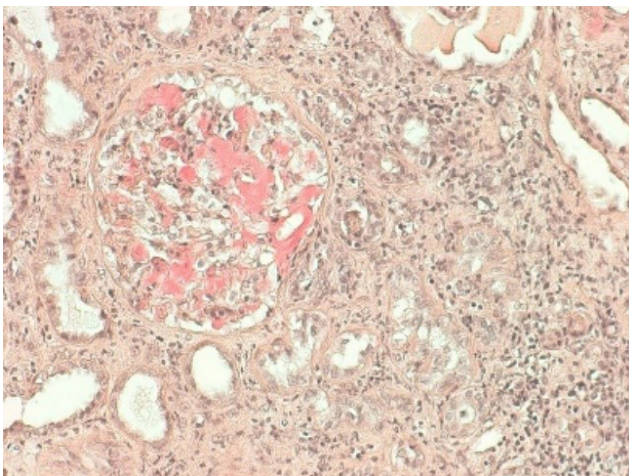


Figure 3a

Immunohistochemistry, x400
Acute tubulointerstitial nephritis with infiltration of T-lymphocytes (CD3 staining).

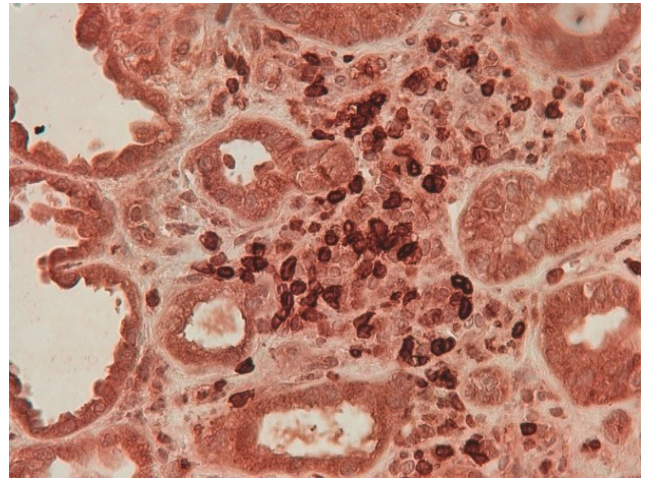
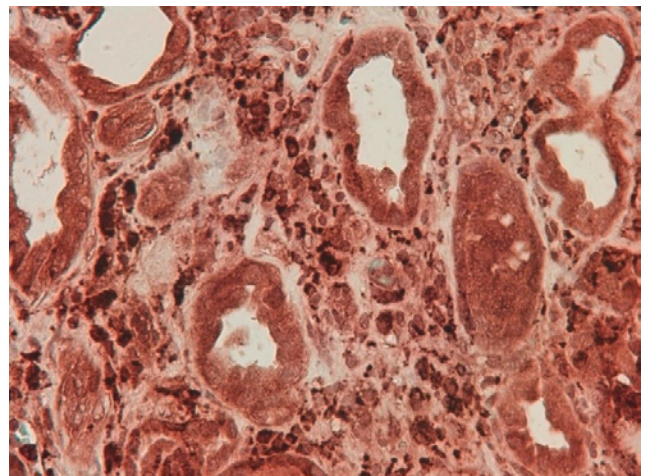


Figure 3b

Immunohistochemistry, x400
Acute tubulointerstitial nephritis with infiltration of T-lymphocytes (CD8 staining).



WBC/mm³), without microscopic hematuria (4 red blood cells/mm³, NR < 17 RBC/mm³). No serum or urinary eosinophilia was found or tested, respectively. Screening for hepatitis B and C viruses and human immunodeficiency virus was negative. Immunological tests (antinuclear and anti-double stranded DNA antibodies, rheumatoid factor, anti-neutrophil cytoplasmic autoantibodies, anti-glomerular antibodies) were also negative. Complement levels and serum immunoglobulin levels were within the normal range. Electrophoresis and immunofixation did not identify the presence of a monoclonal immunoglobulin component in the serum. Renal ultrasonography showed a size asymmetry (168 mm for the left and 98 mm for the right kidney) and a moderate increase of parenchymal echogenicity with normal cortex thickness, without evidence of hydronephrosis. Renal vein thrombosis was excluded by doppler ultrasound. Nivolumab and other nephrotoxic agents (celecoxib and omeprazole) were stopped and oral prednisolone (60 mg/day, at 1 mg/Kg/day) was initiated by the oncological medical team, without clinical or renal function improvement. After 4 weeks of prednisolone (40 mg/day in the last week), our nephrology department was consulted, performing a renal biopsy. Light microscopy demonstrated 11 glomeruli, one of which was globally sclerosed, and some medium caliber vessels. The remaining glomeruli, as well as vessel walls, contained pale, amorphous and eosinophilic deposits (Figure 1) identified as amyloid by Congo red staining (Figure 2) (polarized light not available). Severe AIN with interstitial oedema and infiltration of mono and polymorphic inflammatory cells was found. The interstitial inflammatory infiltrate was predominantly composed of cytotoxic T lymphocytes (CD3+, CD8+) and macrophages (CD68+), with scanty B cells (CD20+) and plasma cells (CD138+) (Figures 3a and 3b). Extensive necrosis of tubular cells in association with tubular inflammatory infiltrate was recognized and no interstitial granulomas were present. Immunofluorescence revealed glomerular and vascular staining for amyloid A protein (Figure 4) but no staining for kappa or lambda light chains. Electron microscopy was not performed. These findings were compatible with AA amyloidosis and acute tubulointerstitial nephritis. The patient was treated with an increased dose of

prednisolone (60 mg daily, at 1 mg/Kg/day) for 4 weeks, without recovery of kidney function or remittance of proteinuria, needing maintenance haemodialysis 3 times per week and dying two months later due to progression of his underlying cancer.

DISCUSSION

We report a case of a patient with metastatic melanoma under ICPI therapy who presented with AKI and nephrotic syndrome. ICPI therapy was presumed to be the cause of both AKI and nephrotic syndrome. Renal biopsy was performed showing AIN and AA amyloidosis. Thus, while AKI may have occurred in the context of AIN-associated ICPI, nephrotic syndrome was likely related to paraneoplastic AA amyloidosis.

Melanoma is the most aggressive type of skin cancer with remarkable propensity for metastatic spreading and is often refractory to anticancer drugs⁸. Nephrotic syndrome can be developed when there is melanoma associated with membranous nephropathy, and is the first manifestation of melanoma in some rare cases¹⁷. Although there is data demonstrating that serum amyloid A (SAA) protein is intensively expressed by malignant melanoma cells and could be a marker for predicting a high risk of tumor progression¹⁸, AA amyloidosis is an unusual complication of melanoma. A successful treatment of the underlying process can lead to the stabilization or improvement of renal function, reduction in protein excretion, and partial resolution of amyloid deposits¹⁹. Cancer cells are known to produce SAA protein²⁰ although AA amyloidosis is rarely associated with solid organ malignancies, metastatic disease and Hodgkin's lymphoma (< 7%)^{21,22}.

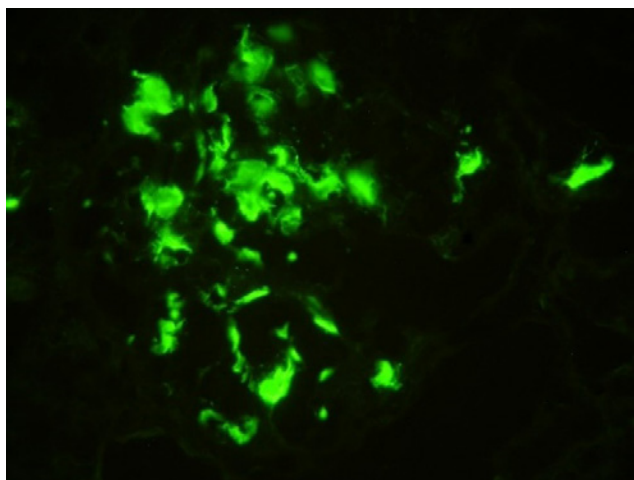
Significant treatment advances for unresectable or metastatic melanoma have occurred in the past few years, with a notable impact on prognosis²³. Ipilimumab (anti-CTLA-4) and nivolumab (anti-PD-1) were the first ICPIs FDA-authorized for the treatment of advanced malignant melanoma.^{24,25} AIN has been described as the most common kidney lesion related to ICPI therapy and there have been case reports of AIN caused by ipilimumab and nivolumab treatment^{15,26-31}. Clinical and histologic features of ICPI-induced AIN are similar to other causes of AIN¹⁵. ICPI-associated AKI has been more frequently reported to occur late after drug initiation (after several months), unlike classic drug-induced AKI, suggesting an alternative mechanism¹⁵. However, the pathophysiology of renal toxicity is still poorly understood and some cases with toxicity occurring after only 21 days of drug initiation¹⁵ have been reported. Currently the mechanism proposed purports that the delay which is seen between drug initiation and AKI development reflects the immunological process of tolerance loss against endogenous kidney antigens whose exposure is induced by ICPI therapy³². It is important to exclude the possibility that AIN was caused by a concomitant medication with known association with AIN rather than an ICPI. A proton-pump inhibitors (omeprazole) and a nonsteroidal anti-inflammatory drug (celecoxib) were started by our patient two months prior of AKI development, making a causal relationship less likely³³.

Nephrotic syndrome can be associated with ICPI therapy⁴, with only one case of AA amyloidosis as a side-effect described in literature³¹. This patient had partial renal function recovery after

Figure 4

Immunofluorescence, x400

Presence of amyloid A protein in glomeruli and arterioles.



pembrolizumab (anti-PD 1) discontinuation and steroid treatment (methylprednisolone 1 mg/kg)³¹. In this case, infliximab (anti-TNF alpha) was also used, due to refractory colitis which can also contribute to renal recovery³¹. Infliximab or other oncologic therapies were not used in our patient.

These multiple possible diagnoses highlight the requirement of renal biopsy for patients with kidney dysfunction in the setting of cancer and ICPI therapy, because a misleading diagnosis may lead to undue therapy discontinuation and high-dose steroid regimen, which carries additional risks and delays the start of appropriate treatment.

In our case, renal biopsy was important to confirm diagnosis. Firstly, we assumed that the clinical picture could be fully explained by nivolumab treatment. Cessation of ICPI and steroid therapy did not result in renal function recovery. Alternative therapies, such as infliximab and mycophenolate mofetil, have been described, but data pertaining to their use is too scarce¹¹ and therefore we have decided to perform a renal biopsy. Histology results showed not only AIN, secondary to immunotherapy, but also AA amyloidosis that was attributed to be a complication of metastatic melanoma, rather than ICPI therapy. In most patients with malignancy-associated AA amyloidosis, the course of proteinuria typically parallels that of the underlying malignancy, with remission of nephrotic syndrome following successful malignancy treatment². This is congruent with our patient, whose proteinuria continued to worsen and who ultimately died due to melanoma progression.

We emphasize the utility of a urinalysis before the initiation of PD-1 inhibitor, which unfortunately was not available in our patient. The presence of proteinuria in a prior urinalysis would have reinforced the diagnosis of AA amyloidosis associated with melanoma. The lack of such important pre-treatment clinical information reinforces the common dilemma in clinical practice of differentiating kidney injury of paraneoplastic cause from cancer treatment toxicity.

CONCLUSION

Given the increasing use of immunotherapies, nephrologists should be aware of their potential immune-related nephrotoxicity. In the setting of malignant tumor and ICPI therapy, patients with urinalysis and kidney function assessment should be closely monitored, to allow for rapid recognition of kidney injury and early intervention.

Disclosure of potential conflicts of interest: none declared

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